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THE RAPIDITY AND PERSISTENCE OF THE ACTION OF DIGITALIS ON HEARTS SHOWING AURICULAR FIBRILLATION.[1]

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The fact that digitalis requires many hours or even days to affect the heart when given in the usual doses, has been perhaps the chief disadvantage in the use of the drug in cases of heart disease in which prompt action is urgently indicated. It is well known that repeated doses must be given before the action of the drug manifests itself, and it is often difficult to determine accurately when the action begins. There has also been considerable discussion as to how long the drug remains effective after its administration is stopped, a point of important bearing on the so-called cumulative action of the drug.

In order to gain further knowledge regarding these questions, the effect of large single doses of digitalis has been observed on a selected group of patients suffering from a form of cardiac disorder which is definitely influenced by the drug. All the cases studied were demonstrated by electrocardiograms to suffer from either auricular fibrillation or auricular flutter, and in all the ventricular rate was abnormally rapid. Care was taken in every case to make sure that the patient was not under the influence of digitalis when the large dose was administered, either by the history, or the statement of the physician sending the patient into the hospital, or by a period in the hospital of at least ten days without the administration of the drug.

Digitalis was given by mouth in the form of the tincture and the dose was regulated according to the method worked out by Eggleston.[2] The underlying principle of this method is to give in one or several frequent doses the entire amount of the drug which may be expected to produce the maximum therapeutic effect. The tincture of digitalis used was purchased from a reliable manufacturer and each lot of the drug was standardized by the "cat method," described by Hatcher and Brodie.[3]

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[1] Read before the Association of American Physicians, Atlantic City, June 17, 1919.

[2] Digitalis Dosage, Arch. Int. Med., 1915, xvi, 1.

It was found that 1 c.c. of the tincture injected intravenously was approximately the lethal dose for one kilo of body weight of the cats used, and following Eggleston's results, 0.15 c.c. was given for each pound of body weight of the patients. The dose, amounting to 15 c.c. per hundred pounds, was the maximum, and was usually given as a single dose, although in some of the earlier cases the dose was divided into three or more parts and given four to six hours apart. The clinical results obtained in giving large single doses of the drug to about 100 patients have been convincing of the correctness of Eggleston's work. This will be demonstrated also by the cases tabulated in this paper. The doses usually ranged from 15 c.c. to 25 c.c. of the tincture.

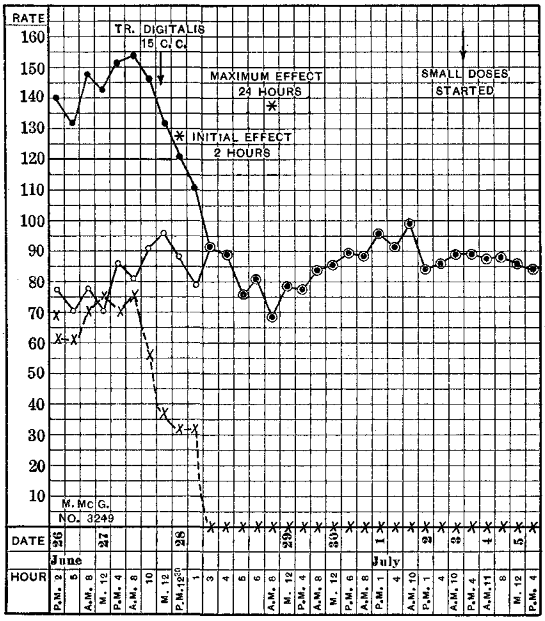

CHART I.—Case 9 of Table. Mitral stenosis and auricular fibrillation. The upper solid line indicates the heart-rate counted by means of the stethoscope placed over the apex-beat. The lower solid line indicates the radial pulse-rate. The broken line indicates the pulse deficit or the number of cardiac contractions that could be heard per minute, which produced no palpable pulsation in the radial artery. The time when the single dose of digitalis caused the initial and maximum effects are indicated. The increase in the rate of the radial pulse and the fall in the pulse deficit with the decrease in the heart-rate are well shown. Initial effect in two hours. Maximum effect in twenty-four hours. Duration of effect not determined.

The patients forming the basis of this paper were studied during continuous rest in bed. The heart rate was counted several times a day by a member of the medical staff, using the stethoscope over the heart, for a number of days whenever the withholding of the drug seemed justified. The radial pulse was also counted, and these findings, together with the pulse deficit (the difference between the heart and radial rates), were charted. After the digitalis was given similar counts were frequently made, in some cases at fifteen-minute intervals, for several hours. The results of three observations are shown in the accompanying charts.

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[3] Biological Standardization of Drugs, Am. Jour. Pharm., 1910, lxxxii, 360.

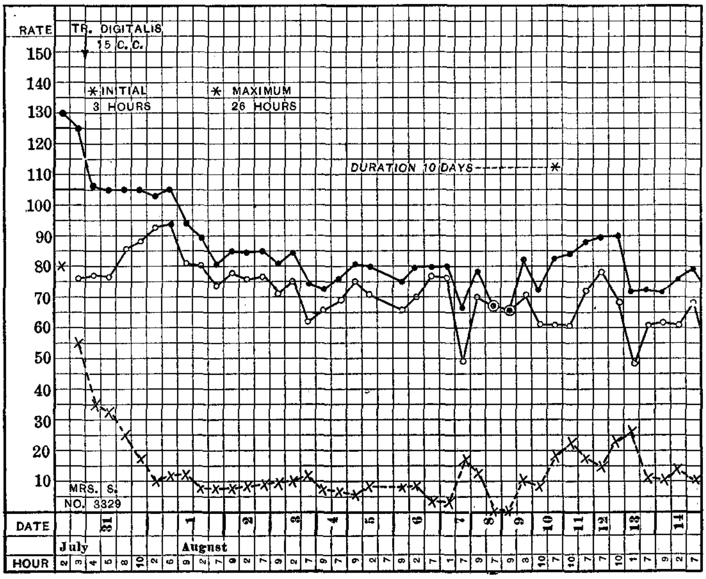

Chart II.—Case 11 of Table. Mitral stenosis and insufficiency, chronic myocarditis and auricular fibrillation. The three lines have the same significance as those in Chart I. The time when digitalis began to be ineffectual is indicated by the increase in the heart-rate which began ten days after the administration of digitalis. Initial effect in three hours. Maximum effect in twenty-six hours. Duration of effect ten days.

The well-known effect of digitalis in slowing the ventricular rate in cases of auricular fibrillation was used as indicating the action of the drug, and practically all of the cases included in this paper showed an abnormally high ventricular rate before digitalis was given. Two cases of auricular flutter are exceptions to the foregoing procedure, and here the disappearance of flutter, as demonstrated by electrocardiograms, was taken as evidence of digitalis action.

Twenty-six cases were studied and tabulated.

In 16 cases the observations were made at intervals sufficiently frequent after the single dose of the drug was given to determine accurately the time when the digitalis became effectual. The drug was considered to have affected the heart when the ventricular rate first became slower than it had been at any time previous to the administration of digitalis and when the ventricular slowing continued, so that the rate of the ventricles assumed a definitely new level. In 2 cases the permanent disappearance of auricular flutter was taken as the indication that the drug had affected the heart. In all of the 16 cases so observed the heart was affected by digitalis in from two to five hours after the oral administration of a single large dose of the tincture.

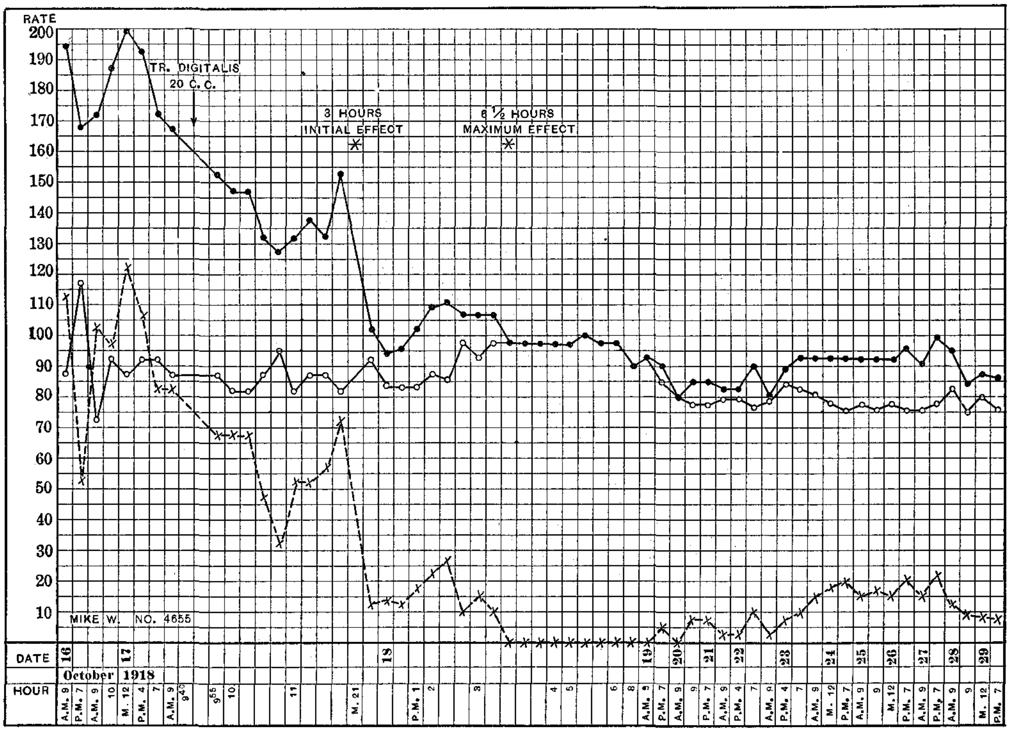

Chart III.—Case 25 of Table. Syphilis, chronic myocarditis and aortitis. The three lines have the same significance as in Chart I. Single dose of 20 c.c. of the tincture given. Initial effect in three hours. Maximum effect in six and a half hours. Heart-rate remained slow for twenty-two days.

The maximum effect of digitalis was considered to have occurred when the ventricles attained approximately their slowest rate and when the pulse deficit had disappeared or reached its lowest count. It was usually quite clear when the maximum effect occurred, but in some cases in which frequent heart-rate counts were not carried on long enough the maximum effect can only be approximated. The charts from the 26 cases studied indicate there is some difference in the length of time required for a single large dose of digitalis to produce the maximum effect on cases of auricular fibrillation, and the cases fall into two groups.

THE EFFECT OF A MASSIVE DOSE OF DIGITALIS ON CASES OF AURICULAR FIBRILLATION.

	No.	Sex.	Age.	Wt.	Diagnosis.	Dose.	Heart-rate.			Duration.
							Before.	Onset time.	Maximum effect.	
1	2608	M.	62	124	Arterial sclerosis; mitral insufficiency; chronic nephritis	17 c.c.	85	?	60, 24 hr.	7 days.
2	2178	F.	52	127	Arterial sclerosis; mitral insufficiency; chronic nephritis	18.5 c.c. in 4 doses	120	?	80, 20 hr.	8 days small doses started
3	2567	M.	48	172	Mitral stenosis and insufficiency	22 c.c. in 3 doses	160	106, 13 hrs.	80, 23 hr.	10 days.
4	2484	F.	49	151	Mitral stenosis and insufficiency; chronic nephritis	22 c.c. in 3 doses	142	105, 5 hrs.	92, 24 hrs.	6 days small doses started.
5	2589	M.	57	190	Mitral insufficiency; myocarditis; chronic nephritis	29 c.c. in 3 doses	135	?	76, 15 hrs.	3 days small doses started.
6	2819	M.	72	137	Arterial sclerosis; chronic nephritis	15 c.c. in 3 doses	130	?	90, 24 hrs.	8 days small doses started.
7	3115	F.	45	140	Myocarditis; chronic alternans; auricular flutter	20 c.c.	148	102, 3¼ hrs.; flutter changed to fibrillation	90, 24 hrs.	13 days.
8	3132	M.	63	110	Arterial sclerosis; chronic nephritis	6 c.c.	132	80, 3 hrs.	80, 3 hrs.	5 days small doses started.
9	3249	F.	35	106	Mitral stenosis	15 c.c.	145	120, 2 hrs.	68, 24 hrs.	5 days small doses started.
10	3257	M.	57	138	Arterial sclerosis; myocarditis; chronic nephritis	9.5 c.c. 5 days after 19 c.c.	Flutter replaced by normal rhythm in 3½ hrs. after 9 days in hospital.			
11	3329	F.	36	100	Mitral stenosis and insufficiency; myocarditis	15 c.c.	130–140	105, 3 hrs.	80, 26 hrs.	11 days.
12	3358	F.	47	110	Mitral stenosis and insufficiency; cystic goitre	15 c.c.	130–160	110, 3 hrs.	85, 22 hrs.	8 days.
13	3466	M.	54	156	Arterial sclerosis; myocarditis	10 c.c., 5 c.c., 3 days later	120	?	82, 18 hrs.	13 days after 2d dose.
14	3494	M.	37	135	Mitral stenosis and myocarditis	20 c.c.	120–150	?	84, 20 hrs.	5 days, 2d dose given.
15	3530	F.	49	130	Exophthalmic goitre; myocarditis	20 c.c.	110–125	?	95, 24 hrs.	6 days.
16	3741	F.	43	178	Mitral insufficiency	18 c.c.	112–160	90, 5 hrs.	80, 8 hrs.	2 days mechanism became normal.
17	3757	M.	49	139	Arterial sclerosis; myocarditis; mitral insufficiency	20 c.c.	120	108, 3 hrs.	87, 14½ hrs.	9 days, 2d dose given.
18	3937	F.	42	122	Mitral stenosis and insufficiency	15 c.c.	75–135	60, 3 hrs.	38, 21 hrs.	15 days.
19	4018	F.	60	74	Mitral stenosis and insufficiency	6 c.c.	150–165	114, 2 hrs.	100, 21½ hrs.	4 days death.
20	4102	F.	23	132	Mitral stenosis and insufficiency; aortic stenosis	6 c.c.	95–115	80, 2 hrs.	55, 6 hrs.	10 days patient discharged
21	4190	M.	62	121	Myocarditis and chronic nephritis	15 c.c.	120–128	?	91, 8 hrs. 81, 26 hrs.	9 days patient discharged
22	4230	F.	54	198	Arterial sclerosis; myocarditis; chronic nephritis	10 c.c. 2d dose 10 c.c.	175–180 150–175	160, 4½ hrs. 105, 5 hrs.	120, 22½ hrs. 90, 18 hrs.	30 hrs., 28 hrs.
23	4261	M.	42	168	Myocarditis; syphilis	15 c.c.	120–150	?	70, 24 hrs.	4 days.
24	4449	M.	40	120	Mitral stenosis and insufficiency	20 c.c.	135–160	118, 3 hrs.	112, 7 hrs.	6 days.
25	4655	M.	48	165	Myocarditis; syphilis; aortitis	20 c.c.	167–207	102, 3 hrs.	96, 6½ hrs.	22 days patient discharged
26	4977	F.	37	?	Mitral stenosis and insufficiency; myocarditis	15 c.c.	130–140	110, 2¼ hrs.	70, 9 hrs.	4 days patient discharged.

In the first group of 19 cases the maximum effect of the drug occurred in from fifteen to twenty-six hours. In a second smaller group of 6 cases the maximum effect occurred in from six to nine hours. The cause of the difference between the two groups is not apparent. In a case of auricular flutter in which the normal cardiac rhythm supervened after digitalis was given no statement as to the maximum effect can be made.

In order to determine the length of time which the drug controlled the heart the patients were kept constantly in bed and the ventricular rates were counted by the stethoscope several times a day. When the ventricular rate began to accelerate and the pulse deficit to increase the drug was considered to have begun to be ineffectual. At this time another dose of digitalis, usually half the amount originally given, was followed by a prompt fall in the ventricular rate and in the pulse deficit. The rise in the ventricular rate was practically always accompanied by an increase in the symptoms of cardiac inefficiency.

In 12 cases in which the time when the drug began to be ineffectual was clearly indicated, digitalis affected the heart for from four to fifteen days, the effect lasting on an average of nine days and six hours. In 1 case the ventricular rate remained slowed for twenty-two days, when the patient was discharged from the hospital without receiving another dose of the drug, although the primary effect had been very striking. In another case the ventricular rate began to accelerate thirty and twenty-eight hours respectively after each dose of 10 c.c. of the tincture, given several days apart. In the remaining 12 cases no statement regarding the duration of the effect can be made, as subsequent doses of the drug were given before the effect of the initial dose had begin to diminish, or, as in 1 case in this series, the patient died four days after the initial dose.

From this series of cases it may be stated, however, that although the effect of a single large dose of the tincture of digitalis on the heart is not constant, it usually lasts from four to fifteen days, and averages nearly ten days.

The persistence of the action of digitalis is of considerable practical importance, and has been the subject of several investigations. Hatcher[4] has shown that various digitalins vary in their persistence in experimental animals and that the persistence also varies markedly in different animals. He showed that the effects of digitonin and digitalis persist longer than do those of the other digitalins in common use, especially in cats. He found that the effects of a single large dose of these drugs, administered intravenously, may persist for a full month. Cohn, Fraser and Jamison[5] investigated this subject, determining the persistence of the drug administered orally to patients by the change in the T-wave of the electrocardiogram. They found that this change, which was brought about by digitalis, persisted for from five to twenty-two days after the administration of the drug was stopped. Although this method of determining the effect of digitalis was not consistently followed in our series of cases, the impression was gained from several cases so studied that the return of the T-wave of the electrocardiogram to the form present before digitalis was given occurred a day or two later than the acceleration of the ventricular rate.

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[4] The Persistence of Action of the Digitalins, Arch. Int. Med., 1912, x, 268.

[5] The Influence of Digitalis on the T-wave of the Human Electrocardiogram, Jour. Exp. Med., 1915, xxi, 593.

Eggleston[6] has also been among those who have studied the duration of digitalis action in man. He determined the length of time that various cardiac disturbances produced by the drug persisted and found that coupled beats (regularly recurring premature ventricular contractions) persisted for from four to twelve days after digitalis was discontinued, while other disturbances of the cardiac mechanism caused by digitalis persisted for a shorter length of time.

A matter that has been frequently discussed regarding the effect of digitalis when administered by mouth has been the question of the rapidity of its absorption from the alimentary tract. The study of our series of cases seems to throw some light upon this subject. It has been customary to consider the absorption of digitalis from the alimentary canal as irregular, slow and uncertain and the factor of absorption has been called upon to explain differences in the amounts of the drug required to produce the same effects in different individuals. Recently, Wedd[7] found there was a wide difference in the amounts of digitalis necessary to produce certain toxic effects in different individuals, the individual variation being from 20 c.c. to 100 c.c. of the tincture given in large but not single doses. The variation, he believes, is due to variations in absorption. There is, no doubt, definite difference in the rapidity of absorption of different digitalis preparations, as Haskell, McCants and Gardner[8] have shown experimentally, and they find that the tincture is better absorbed from the gastro-intestinal tract than the infusion, and is equally as well absorbed as other preparations.

Eggleston concluded from his study of the effects of large doses of the drugs that digitonin was more completely absorbed than digitalis, but, nevertheless, he found that both of these preparations are probably rapidly and fairly uniformly absorbed from the alimentary canal of man.

The fact that a single large dose of the tincture of digitalis uniformly affected the heart of all of the cases in our series in which its initial effect could be determined in from two to five hours, offers a strong argument for the fairly rapid and uniform rate of absorption from the alimentary tract of patients with heart disease. It is true that the maximum effect did not show so uniform a relation to the time of administration, but it seems probable that factors other than absorption may have been responsible for the variations in the time required for the maximum effect to occur.

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[6] Clinical Observations on the Duration of Digitalis Action, Jour. Am. Med. Assn., 1912, lix, 1352.

[7] Observations on the Clinical Pharmacology of Digitalis, Bull. Johns Hopkins Hosp., 1919, xxx, 131.

[8] The Rate of Absorption of Various Digitalis Preparations from the Gastro-intestinal Tract, Arch, Int. Med., 1916, xviii, 235.

It is this rapid and uniform rate of action of the drug when administered in large single doses as herein described, which especially commends the use of digitalis in this manner therapeutically. It is felt that further studies are required before such large doses as were given should be recommended for general use, especially when patients are not under constant observation in hospitals. But the method has been sufficiently tried so that it seems entirely justified whenever rapid digitalis action is strongly indicated, and our experience leads us to believe that it is a much safer method of obtaining rapid digitalis action than the intravenous administration of digitalis bodies, especially strophanthin. Nearly all the cases reported in this series showed very striking clinical improvement within a few hours after the administration of the single large doses of the tincture of digitalis. It is particularly on this account that it is felt that Eggleston's conclusions as to the dosage of the drug are essentially correct.

SUMMARY. A series of 26 cases of auricular fibrillation or flutter are reported, to which large single doses of the tincture of digitalis were administered by mouth. The drug used was standardized and was usually given in doses ranging from 15 c.c. to 25 c.c.

The study of these cases demonstrates that such doses of digitalis affect the heart of cases of auricular fibrillation or flutter at a relatively constant time after administration, in from two to five hours, indicating that the drug is absorbed from the alimentary tract at a fairly rapid and uniform rate. The series of cases also demonstrates that the maximum effect on the heart is usually obtained in about twenty-four hours and generally continues to be effectual for from four to fifteen days, or on an average of nearly ten days.